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Division of Dockets Management (HFA –305)
Food and Drug Administration
5630 Fishers Lane - Room 1061
Rockville, MD 20852

RE: *Class II Special Controls Guidance Document: Hepatitis A Serological Assays for the Clinical Laboratory Diagnosis of Hepatitis A Virus [Docket 2004D-0385]*

Dear Sir or Madam:

Abbott Laboratories submits the following comments regarding FDA draft guidance document "Hepatitis A Serological Assays for the Clinical Laboratory Diagnosis of Hepatitis A Virus; Class II Special Controls Guidance Document," published in the Federal Register on September 30, 2004 at 69 FR 58448.

Thank you for the opportunity to provide these comments. Abbott is a manufacturer of hepatitis assays for diagnostic use and blood screening and one of the first commercial manufacturers of a diagnostic hepatitis A serological assay. With few exceptions, we agree that the special controls outlined in the document support the clinical use of hepatitis A (HAV) serological assays. We do, however, respectfully request that FDA reconsider the inclusion of the post vaccination and prevalence studies in the special controls document, in light of the "least burdensome" principles of the Food and Drug Administration Modernization Act of 1997 (FDAMA) and the intended use of the assay.

Least burdensome is defined as "a successful means of addressing a premarket issue that involves the most appropriate investment of time, effort, and resources on the part of industry and FDA."[1] The least burdensome guidance document further states, "information that is scientifically interesting but not necessary for purposes of determining substantial equivalence should not be part of a submission."[2]

[1] FDA, The Least Burdensome Provisions of the FDA Modernization Act of 1997; Concept and Principles; Final Guidance for FDA and Industry at 2 (Oct. 4, 2002).
[2] *Id.* at 13.

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Post vaccination immunity

The special controls guidance document recommends testing "specimens from individuals that have been vaccinated against HAV" to address "testing for immunity due to vaccination." Because FDA's companion proposed rule does not recognize testing for immunity due to vaccination as an intended use of hepatitis A serological assays and it is not common clinical practice to conduct post vaccination testing we question the necessity of conducting such studies and whether such testing is consistent with the "least burdensome" principles of FDAMA.

FDA's companion proposed rule identifies HAV serological assays as devices "used for testing specimens from individuals who have signs and symptoms consistent with acute hepatitis or for determining if an individual has been previously infected with hepatitis A virus" and "detection of these antibodies aids in the clinical laboratory diagnosis of an acute or past infection by hepatitis A virus."[3] It is not common clinical practice to conduct post HAV vaccination testing because of the high immunogenicity of the vaccine.[4 5 6 7] According to the Advisory Committee on Immunization Practices (ACIP), "[p]ost vaccination testing is not indicated because of the high rate of vaccine response among adults and children[8]."

We recognize FDA's Microbiology Devices Advisory Panel Meeting, February 12, 1998, included a discussion of post HAV vaccination testing. However, the record suggests much of this discussion focused on the use of commercial assays versus home brew assays in the development of HAV vaccines[9] and many of the statements were in the context of "***if*** the clinical indication for this new assay is to determine immunity[10]" (emphasis added). Even Dr. Field's statement, "I think there is some utility for a more sensitive test as it applies to the post-vaccine setting" was in the context of "evaluation of vaccines," not a clinical use to determine immunity post vaccination.[11] It was further

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[3] 69 Fed. Reg. 58374 (2004) (to be codified at 21 C.F.R. § 866.3310) (proposed Sept. 30, 2004).
[4] CDC, Prevention of Hepatitis A Through Active or Passive Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP)," MMWR 1999; 48 (No. RR-12); 1-37.
[5]CDC, Sexually Transmitted Diseases Treatment Guidelines –2002, MMWR 2002; 51 (No. RR06); 1-80.
[6] Viral Infections and Treatment at 271 (Helga Rubsamen-Waigmann et al. eds., 2003).
[7] Jennifer Cuthbert, *Hepatitis A: Old and New*, 14 (1) Clin. Microbiol. Rev. 38, 46 (2001).
[8] CDC, Prevention of Hepatitis A Through Active or Passive Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP)," MMWR 1999; 48 (No. RR-12); 1-37.
[9] Microbiology Devices Panel Meeting, Medical Advisory Committee Meeting to discuss characterizing performance of tests for the diagnosis and monitoring of viral hepatitis (Feb. 12, 1998). Dr. Ticehurst is quoted as saying, "they took a commercially available total ant-HAV assay and changed the configuration of it, so that was basically a home brew assay." Dr. Hollinger is quoted as saying, "almost all of these vaccine studies have been in-house studies."
[10] Microbiology Devices Panel Meeting, Medical Advisory Committee Meeting to discuss characterizing performance of tests for the diagnosis and monitoring of viral hepatitis (Feb. 12, 1998). Dr. Edelstein is quoted as saying, "if the clinical indication for this new assay is to determine immunity, then I think the only way you could establish that is by doing a clinical trial that correlates the results of the assay with immunity."
[11] Microbiology Devices Panel Meeting, Medical Advisory Committee Meeting to discuss characterizing performance of tests for the diagnosis and monitoring of viral hepatitis (Feb. 12, 1998).

noted at this meeting, that the ACIP December 1996 issued recommendations for hepatitis A vaccines are for no post-vaccination testing.

Subsequent to FDA's 1998 Microbiology Devices Advisory Panel Meeting, the Centers for Disease Control, in 1999, issued an updated version of the ACIP recommendations pertaining to HAV vaccination. Again, the ACIP recommended that "post vaccination testing is not indicated because of the high rate of vaccine response among adults and children."[12] More recently issued travel guidance by the CDC maintains this position, specifically stating, "postvaccination testing for serologic response is not indicated."[13]

We respectfully request that FDA reconsider the inclusion of the HAV post vaccination study in the special controls document in view of the following: (1) the intended use of HAV serological assays, (2) FDA's proposed companion rule does not recognize post vaccination immunity testing, (3) the ACIP does not recommend such testing, and (4) FDA's "least burdensome" principles.

Prevalence

The guidance recommends establishing the prevalence of HAV antibodies in a normal population (healthy individuals without symptoms). Since prevalence studies are conducted to understand the disease, itself, the relationship of such a study to the safety and effectiveness of the diagnostic hepatitis A serological assay is unclear. Disease prevalence studies are conducted by the Centers for Disease Control, such as Sentinel Counties Surveillance for acute viral hepatitis[14]. Further, since age and geographic distribution influences the outcome of the prevalence study, variable results, based on population distribution, would be expected. We respectfully request that FDA provide additional rationale for the prevalence study, in relation to the intended use of the diagnostic assay and mitigation of identified risks or reconsider, under the least burdensome principles, the necessity of the study.

Matrices other than serum

We support the testing of anticoagulants for devices indicated for use in matrices other than serum, but recommend characterizing this testing as interference testing. Thus, we recommend moving anticoagulant testing from the sections on "reproducibility" and "other analytical studies" to the section on "interference." In the "interference" section, we suggest adding the following underlined text to the sentence beginning "[p]otential sources of interference..."

Potential sources of interference can include compounds normally found in serum, such as triolein (triglycerides), hemoglobin, bilirubin, and serum albumin, as well as potential serum-based interference by rheumatoid factor (RF), anti-nuclear antibodies (ANA), and heterophilic antibodies, and for devices indicated for use in matrices other than serum, anticoagulants (e.g., EDTA or sodium heparin).

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[12] CDC, Prevention of Hepatitis A Through Active or Passive Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP)," MMWR 1999; 48 (No. RR-12); 1-37.
[13] CDC, Yellow Book 2003-4: Diseases: Hepatitis, Viral, Type A, Travelers Health (http://www.cdc.gov/travel/diseases/hav.htm accessed on Dec. 9, 2004).
[14] Beth P. Bell et al., *The Diverse Patterns of Hepatitis A Epidemiology in the United States – Implications for Vaccination Strategies,* 178 J. Infect. Dis. 1579-84 (1998).

Labeling

User training, including documentation and proficiency, is addressed as part of design validation, and not necessarily in product labeling. To reflect the management of training as part of design validation we recommend the following change to the section "directions for use."

"Instructions ~~should~~ may encourage local/institutional training programs..."

We appreciate the opportunity to comment on this draft guidance document. Should you have any questions, please contact me at (847) 937-8197 or by facsimile at (847) 938-4422.

Sincerely,

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